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Optimizing the Allocation of Vaccines in the Presence of Multiple Strains of the Influenza Virus

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Abstract. During the annual flu season, multiple strains of the influenza virus are often present within a population. It is a significant challenge for health care administrators to determine the most effective allocation of multiple vaccines to combat the various strains when protecting the public. We employ a mathematical model, a system of differential equations, to find a strategy for vaccinating a population to minimize the number of infected individuals. We consider various strengths of transmission of the disease, availability of vaccine doses, vaccination rates, and other model parameters. This research may lead to more effective health care policies for vaccine administration.

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1 Introduction

Every year, the influenza virus causes many individuals to become ill; therefore, it is important for healthcare professionals to determine the best method of vaccination for each season. As an infected individual sneezes, coughs, or talks, the influenza virus may be excreted and therefore spread the disease to other individuals [6]. After someone becomes infected, they eventually recover in most cases. After the recovering, the individual may become infected with a secondary attack, typically from another strain of the virus [1]. Different levels of immunity may alter an individual's susceptibility for a specific strain of influenza; this may cause a difference in the likelihood of an individual becoming infected again during the same season [5].

To determine the best vaccination strategy, the most prevalent strain present during the upcoming season needs to be determined. The three main types among influenza viruses are A, B, and C; however, A and B are the ones which cause epidemics to occur [3]. The C type of influenza virus causes respiratory illnesses that are not epidemics [3].

The influenza vaccine contains two types of influenza A viruses, as well as influenza B virus. The two types of influenza A virus included are H1N1 and H3N2 [3]. The viruses H1N1 and H3N2 have caused human epidemics[6]. To vaccinate against the most prevalent strain for the upcoming season, one needs to understand how the current season's influenza virus will act. To understand this and create the vaccine, healthcare professionals examine the spread of the prominent influenza virus strains during the upcoming influenza season [2].

Previous studies have examined infectious diseases, such as influenza, using mathematical modeling and differential equations. The first model used to examine infectious diseases was the SIR model [4]. The state variables used were S for the susceptible class, I for the infectious class and R for the recovered class (see, for example, [8, 11, 12]). Ordinary differential equations are used to represent the population trend through each class, which are given in section 2.

The model used in our study is a variation of the SIR model. There is a point in which the epidemic curve reaches a maximum peak and then declines; this was examined in our model. This occurs because the infected individuals in the population recover and are no longer able to transmit the virus (see, for example, [4, 8]).

Studies have been conducted in which a variation of the SIR model was used. One such study by Stilianakis et al., a variation was used to incorporate several infectious and susceptible classes [10]. In this study, we incorporated several classes of the infectious class. For example, the class $I_{A|B}$ represents that an individual was infectious with strain A given that he/she previously had strain B.

Another example of a model which may be used to examine spread of infectious diseases is the SIS model. This model reflects a population that progresses from susceptible to infectious and back to susceptible, indicating that there is no immunity acquired [9]. Although our model contains only one susceptible class, individuals in our population can get both strains of the virus. This is similar to the SIS model in that individuals can be infected multiple times, albeit with a different strain. In this study, a model was used to ultimately

test what kind of effect varying rates of vaccination would have on different situations with multiple different parameters.

Our mathematical model was created to be useful in choosing an influenza vaccination. The model was analyzed using the mathematical software package `MATLAB`. Several parameters were used to create the model: the number of individuals present, the transmission rate of the disease, the recovery rate, and the vaccination parameter. These parameters were used to represent the possible stages of class progression and are further explained in section 3. When creating the model, it was useful to examine the basic reproductive number for influenza. The basic reproductive number represents the number of secondary infections an individual in a susceptible population may undergo during the infectious phase (see, for example, [10, 11]). Thus, it provides a guide to whether the disease will spread through the population (see, for example, [4, 11, 12]). Section 2 gives more information on the basic reproductive number.

We also examined the relationship between the number of individuals that were ill compared with the availability of vaccines. We attempted to model the vaccination process in such a way to obtain the smallest number of infections. it is important to note that the optimal rate of vaccination is determined by the number of strains of the disease present in a population. If there was only one strain, the optimal way to vaccinate would be to do it immediately. However, with a limited number of doses and no specific number of doses allocated to each strain, the quickest rate of vaccination may not always be the best. In section 2, we explain the SIR model, in section 3 our own model is further explained. In section 4, methodology is given to explain how the model was produced. In section 5, we present the results of our analysis. The paper is concluded with a discussion of these results. The last section of the paper, Appendix: Coding the Simulation, provides further explanation of methodology that includes `MATLAB` syntax.

2 Background Model

The SIR model is the classic model of a population exposed to an infection. It is a compartment model with three classes: the susceptible class, the infectious class, and the recovered class. This is illustrated in the flowchart in Figure 1.

Figure 1: Flow chart representing the trend of a controlled population in which a virus is present. S represents the susceptible class, I represents the infectious class, and R represents the recovered class.

A closed population in one in which the population remains constant, implying that no births or deaths occur. The SIR model is constructed under the assumption that the population is closed. To understand the basic population trend, no vaccines were incorporated into this model.

Differential equations describe the changes in the subpopulations with the state variables $S(t)$, $I(t)$ and $R(t)$ through the processes of infection and recovery:

$$\frac{dS}{dt} = \frac{-\beta SI}{N} \tag{1}$$

$$\frac{dI}{dt} = \frac{\beta SI}{N} - \gamma I \tag{2}$$

$$\frac{dR}{dt} = \gamma I. \tag{3}$$

The total population size is denoted by N. Moreover, the parameters β and γ denote transmission and recovery rates, respectively.

Another important feature of this model is the basic reproductive number, R_0. To reiterate, the basic reproductive number is the average number of secondary infections the first infectious individual gives rise to before they recover. The equation for R_0 using this model is

$$R_0 = \frac{\beta}{\gamma}. \tag{4}$$

R_0 is a threshold parameter that determines, at the start of an outbreak, if the number of infectious individuals, I, is increasing or decreasing. In the case of the SIR model, this is solely determined by the ratio of the transmission parameter to the recovery rate.

When R_0 is greater than 1, initially, each sick individual produces more than one additional infectious person. In other words, the rate of transmission is greater than the rate of recovery, producing a rapid spread of the disease yielding an outbreak. At the beginning of an outbreak, there is a dramatic growth of the infectious class, $I(t)$, at the expense of the susceptible class, $S(t)$.

When R_0 is less than 1, each sick individual produces less than one newly infected person. The rate of recovery is the greater than the rate of transmission leading to a nearly immediate decrease in $I(t)$. The virus spreads too slowly to produce an outbreak.

Thus, $R_0 = 1$ is the threshold of what we consider an outbreak.

Figure 2 depicts a solution of the SIR model in which a population of 1000 people became infected with the flu over time. Here, $R_0 = 5 > 1$. Notice that at the start of the outbreak, individuals are getting infected with the virus quicker than they are recovering from the infection. Eventually, nearly everyone in our population gets infected and S approaches zero, while R approaches N.

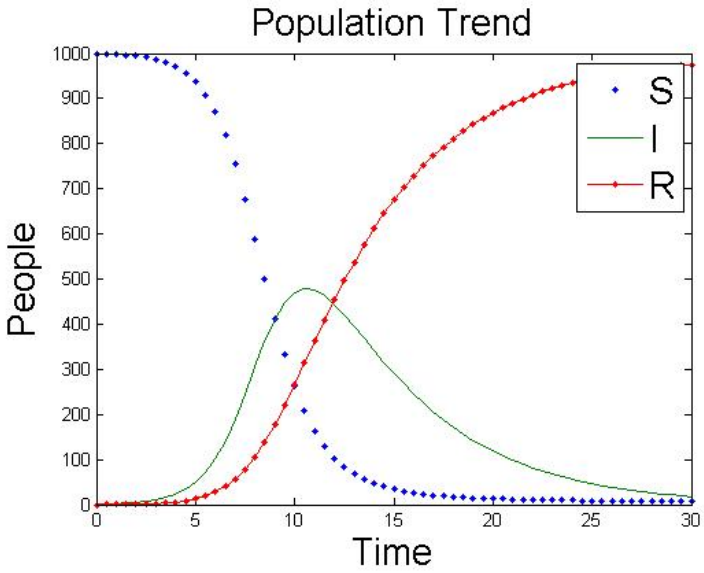

Figure 2: A plot of the subpopulations of the SIR model versus time. The solid curve depict the prevalence, $I(t)$, the dotted curve depicts the number of susceptibles, $S(t)$, while the solid-dot hybrid curve depicts the number of recovered individuals, $R(t)$. The initial conditions of the model are $S(0) = 999$, $I(0) = 1$, $R(0) = 0$, with parameters $N = 1000$, $\beta = 1$, and $\gamma = 0.2$.

3 Model

The key issue in this paper deals with the administration of vaccines against various strains of a virus. In the real world, there is often more than one strain of a virus (we restrict this investigation to two strains), and it usually can't be predicted whether or not one strain will be stronger than the other. Ideally, we could administer an unlimited number of vaccines for each virus strain immediately, thus protecting the entire population against infection. This is not realistically possible due to monetary issues or a lack of supply of vaccine doses. Thus, we set a limited number of doses, v, in our model to simulate this more realistic scenario. The value v is the total number of doses partitioned between both strains A and B. The number of doses allocated to each strain is v_i, such that

$$v = v_A + v_B. \tag{5}$$

If there was only one strain of the virus, the optimal vaccination rate would also be the quickest possible rate, even with a limited supply of doses, for that strain. However, when we consider multiple strains, the fact that healthcare professions do not *a* priori know which strain is stronger, it raises an allocation complication.

Another issue that arises when the vaccines are limited is "wasted" vaccine doses. If it is known that there are two different virus strains moving through a population, many individuals will want to get vaccinated for both. If an individual chooses to get vaccinated

after they have already been infected once, they have the possibility of wasting a vaccine. Normally, people are not tested for which strain was contracted before they are vaccinated again. So, if an individual gets strain A and then gets vaccinated for strain A, the vaccination was essentially useless and is no longer available for an individual who needs it. See, for example, in Figure 3, the transition from R_A to R_{AV}.

To find the optimal rate and distribution of vaccinating against two strains of the flu, we created a new model using a variation of the SIR model. We model the spread of two strains of the flu virus in a closed population, and we incorporate the use of two different vaccines, one to fight each strain. A flowchart to describe each compartment is given in Figure 3.

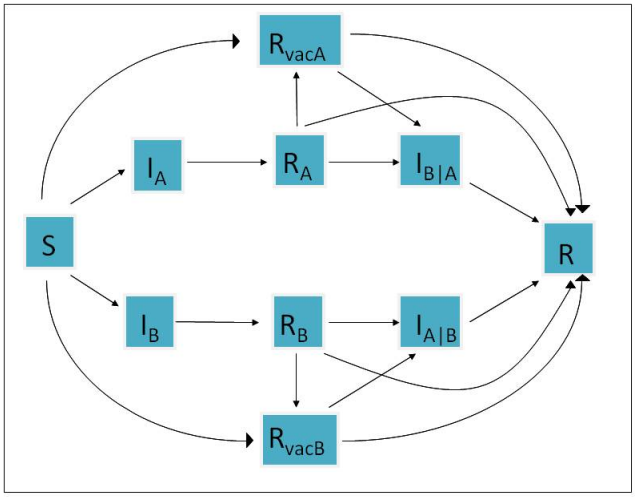

Figure 3: A flowchart representing the population trend through each class of our model. The I_A and I_B classes represent those who initially became infected with strain A and strain B, respectively. The R_A and R_B classes represent those who recovered from those strains. The R_{AV} and R_{BV} classes represents those who were successfully vaccinated against the resepctive strain. The $I_{B|A}$ class represents those who became infected with strain B after recovering from strain A while the $I_{A|B}$ class represents those who became infected with strain A after recovering from strain B. The R class represents those who recovered from both strains.

Our model is a system of nine ordinary differential equations:

$$\frac{dS}{dt} = \frac{-S(\beta_A I_A + \beta_B I_B + \beta_A I_{A/B} + \beta_B I_{B/A})}{N} - S(\nu_A + \nu_B) \tag{6}$$

$$\frac{dI_A}{dt} = \frac{S(\beta_A I_A + \beta_A I_{A/B})}{N} - \gamma_A I_A \tag{7}$$

$$\frac{dI_B}{dt} = \frac{S(\beta_B I_B + \beta_B I_{B/A})}{N} - \gamma_B I_B \tag{8}$$

$$\frac{dR_A}{dt} = \gamma_A I_A - \frac{R_A(\beta_{B/A} I_B + \beta_{B/A} I_{B/A})}{N} - R_A(\nu_A + \nu_B) \tag{9}$$

$$\frac{dR_B}{dt} = \gamma_B I_B - \frac{R_B(\beta_{A/B} I_A + \beta_{A/B} I_{A/B})}{N} - R_B(\nu_A + \nu_B) \tag{10}$$

$$\frac{dI_{A/B}}{dt} = \frac{R_B(\beta_{A/B} I_A + \beta_{A/B} I_{A/B})}{N} + \frac{R_{BV}(\beta_{A/B} I_A + \beta_{A/B} I_{A/B})}{N} - \gamma_{A/B} I_{A/B} \tag{11}$$

$$\frac{dI_{B/A}}{dt} = \frac{R_A(\beta_{B/A} I_B + \beta_{B/A} I_{B/A})}{N} + \frac{R_{AV}(\beta_{B/A} I_B + \beta_{B/A} I_{B/A})}{N} - \gamma_{B/A} I_{B/A} \tag{12}$$

$$\frac{dR_{AV}}{dt} = \nu_A S + \nu_A R_A - \frac{R_{AV}(\beta_{B/A} I_B + \beta_{B/A} I_{B/A})}{N} \tag{13}$$

$$\frac{dR_{BV}}{dt} = \nu_B S + \nu_B R_B - \frac{R_{BV}(\beta_{A/B} I_A + \beta_{A/B} I_{A/B})}{N} \tag{14}$$

The total population is denoted by N. The transmission parameter with respect to strain i is β_i for $i \in \{A, B\}$, the transmission parameter for those obtaining strain A who have already recovered from strain B is $\beta_{A|B}$, and likewise, the transmission parameter for those obtaining strain B who have already recovered from strain A is $\beta_{B|A}$.

The recovery parameter for those recovering from strain i is γ_i. The recovery parameter of those moving from the $I_{A|B}$ class is $\gamma_{A|B}$ while the recovery parameter for those moving from the $I_{B|A}$ class is $\gamma_{B|A}$. Each recovery rate is the reciprocal of the average duration that a person will be infected with the given strain before they recover from it. Each recovery rate has units $time^{-1}$.

The vaccination rate for strain i is ν_i. The average time when an individual would be vaccinated against strain i is $\frac{1}{\nu_i}$. For example, if $\nu_A = 10$, then, on average, each person that enters the population should be vaccinated at $\frac{1}{10}$ time units from when the beginning of the outbreak.

We assumed it is more difficult to contract the second strain of the virus after an individual has already recovered from the first. Also, we assumed it was easier to for an individual to recover from their first infection. We modeled these assumptions using the β and γ values for each strain, as described in the next section.

4 Methodology

We used the software package `MATLAB` (Mathworks, Inc.) to explore different scenarios using our model. The goal was to minimize the total number of individuals infected with either

strain of the virus by altering the vaccination rates. We performed this optimization under different values of R_0. We used three different values in an attempt to illustrate three qualitatively different scenarios: R_0 =1.8, 3, and 10. To get these R_0 values we changed our transmission parameter (β) while keeping the recovery parameter the same. In this way, the average duration of each infection was constant. This was done to see how each R_0 value would alter the total number of infections that occur. See appendix for details on coding the simulation.

To minimize the total number of individuals infected, we set the objective function to be the total number of infections of either strain during the outbreak. This value is computed using the integral

$$\frac{1}{N}\int_0^{t_{end}} S(\beta_A I_A + \beta_A I_{A/B} + \beta_B I_B + \beta_B I_{B/A}) + R_A(\beta_{B/A} I_B + \beta_{B/A} I_{B/A}) + ...$$

$$R_B(\beta_{A/B} I_A + \beta_{A/B} I_{A/B}) + R_{AV}(\beta_{B/A} I_B + \beta_{B/A} I_{B/A}) + R_{BV}(\beta_{A/B} I_A + \beta_{A/B} I_{A/B})\, dt. \quad (15)$$

We obtained this value numerically by using the `ode45` command in `MATLAB`, which uses a 4th-5th order Runge-Kutta method (see `MATLAB`'s documentation for ODE solvers for details). We could then track the objective function's value across many different parameter values of the model and find which conditions achieved the minimum value. The total number of infections during the outbreak is influenced by many factors out of our control, and vaccination rates, which we could modify in a real scenario, so our decision variables were the vaccination rates (ν_A and ν_B).

To analyze the ν values that would minimize the objective function, we utilized two separate methods. We computed the value of the objective function across an array of ν_A and ν_B values, then found which of these values produced the minimum. Second, to visually represent our objective function, we produced contour plots so that we could see where the lowest value of the objective function occurred, which would correspond to the optimal values for ν_A and ν_B.

This process was then repeated for qualitatively different values of R_0^A and R_0^B to see the trends among the ν values with respect to the infection rate. In other words, we could solve the model with various parameters to see how the optimal vaccination rates were affected by the basic reproductive number.

5 Results

5.1 Population Trends

We found optimal vaccination rates using six different combinations of R_0 values for strain A and strain B. We created corresponding graphs of solutions of the model illustrating the subpopulations against time, illustrated in Figure 4.

When both strain A and strain B have an R_0 of 1.8 (Figure 4a), very few infections occur in the time allotted. Since $R_0 > 1$, an outbreak was expected. The result, however, shows

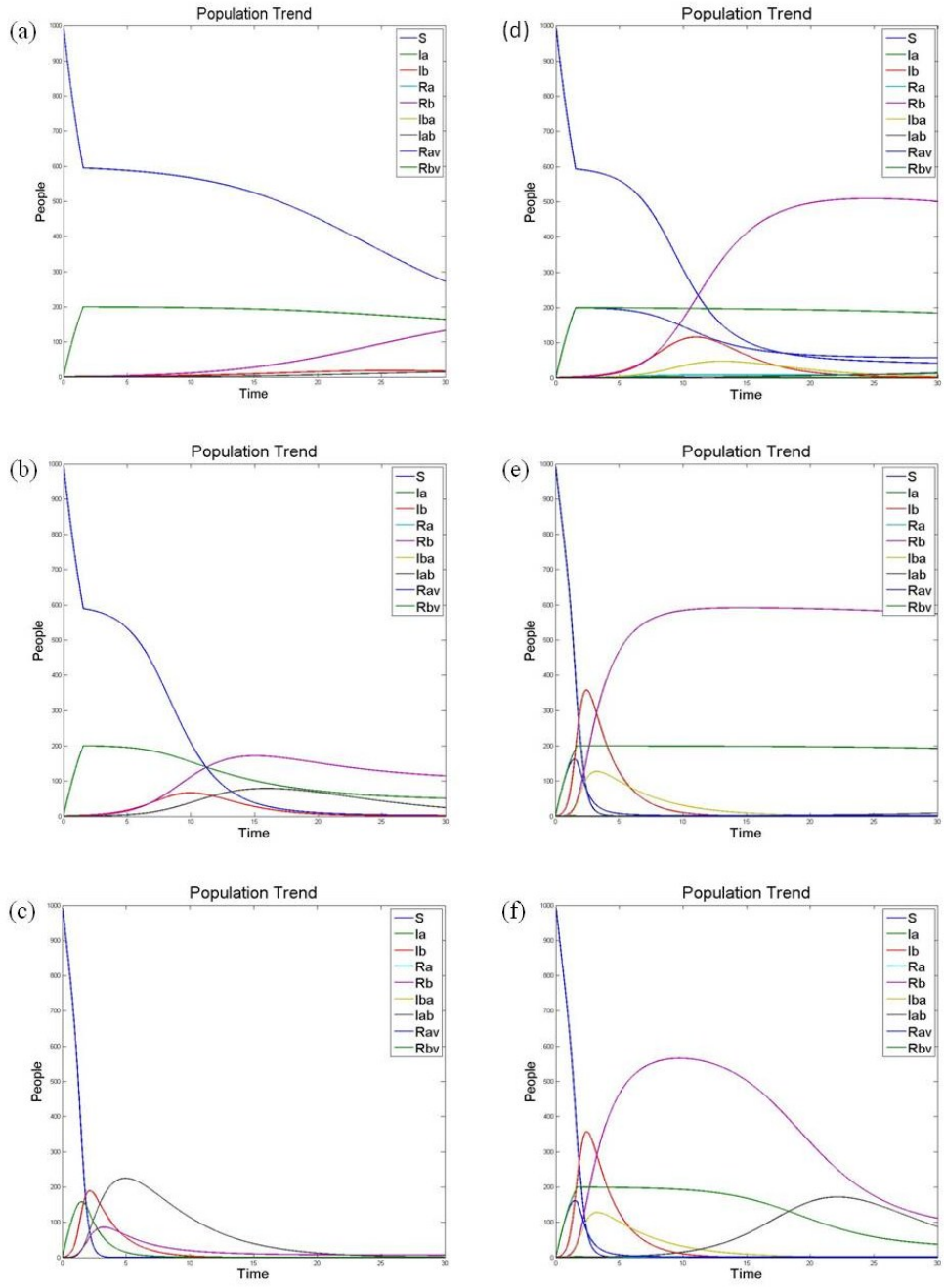

Figure 4: The population trend through each class vs time. Each plot uses a different pair of R_0 values. In (a), (b) and (c), strains A and B have the same R_0, of 1.8, 3, and 10, respectively. Note that only the curves for strain B are visible, as the solutions are identical so the curves overlap. In panel (d), (e) and (f) contain solutions when $R_0^A = 1.8$, $R_0^B = 3.0$ and $R_0^A = 1.8$, $R_0^B = 10.0$ and $R_0^A = 3.0$, $R_0^B = 10.0$, respectively.

that very few infections actually occur. This is due to a high initial vaccination rate, as shown by the steep slope at the beginning of the graph. It can be seen when the vaccination dose limit, v, is reached as the sharp change of population trend in the S, R_{BV}, and R_{AV} classes occur. The limit is reached at about $t = 1.5$.

When $R_0 = 3$ for both A and B (Figure 4b), there are more infections over a smaller amount of time. With a higher R_0 value and a constant vaccination rate, this is to be expected. The sharp change is still easily seen at about $t = 1.5$, where the vaccine doses run out. One interesting thing to note is that the classes with the highest number of people at the end of the run are R_A and R_B. This is attributed to our earlier assumption that it would be more difficult to be infected by a second strain of the virus. Since $\beta_{A|B}$ and $\beta_{B|A}$ are smaller than β_A and β_B, more people are entering R_A and R_B than are leaving. As one can see, a similar result occurs in all of the other figures.

When $R_0 = 10$ for both strains A and B (Figure 4c), a different situation results. The discontinuity in the change of the populations is barely seen, making it difficult to discern when the vaccine doses run out (which occurs around $t = 2$). While the R_A and R_B classes still have the highest portion of the population at $t = 30$, their achieved maxima are less than what is seen in previous scenarios. This is explained by higher β values. These high values also account for R_{AV}, R_{BV}, I_A, and I_B reaching their maxima and quickly decreasing and S approaching zero quickly. Because the γ values for $I_{A|B}$ and $I_{B|A}$ are relatively small, they reach their highest maximum values and stay larger longer compared with the other graphs.

The dynamics are substantially more varied when the R_0 values for A and B are different (Figures 4d-f). To simplify the terminology, we will refer to the graphs using their R_0 values in parentheses, with the R_0 value for A as the first entry and the R_0 value for B as the second.

In the graph (1.8, 3), there are several interesting features (Figure 4d). Firstly, half of the population ends up in the class R_B. R_B increases to a high number due to a low β_A and an even lower $\beta_{A|B}$, meaning more people are entering R_B than leaving it. Secondly, R_{BV} remains fairly constant upon reaching 200, while R_{AV} decreases to about 50. R_{BV} remains constant for the same reason, while R_{AV} decreases because of the higher value of $\beta_{B|A}$. Thirdly, both R_{AV} and R_{BV} increase at the same rate. This could be explained by the fact that vaccinations are only being administered until $t = 1.5$ and the rates of infection are not significantly different enough to majorly effect infection of the population during such a small time period. Lastly, although the curves for I_A and R_A are low, people are still being infected by strain A, albeit much less frequently than strain B.

In the graph (1.8,10) (Figure 4e), there are similar trends to (1.8,3), however, there are several fundamental differences. The first major difference is the dynamics occur much faster. The same phenomena are observed, just over a much smaller time period due to the large R_0 value of strain B, quickening the rates of infection and recovery. The second difference is that the class I_β has a higher maximum value and exceeds that of the vaccinated classes, again, attributed to the large R_0 value of B. People become infected quickly enough that even fast vaccination rates cannot keep people from entering I_B. The most important distinction

occurs among the vaccination classes. Just as in (1.8,3), R_{BV} reaches 200 and stays fairly constant after $t = 1.7$. However, although R_{AV} begins at the same rate as R_{BV}, R_{AV} drops off before reaching 200. While it may appear that there were fewer vaccines administered for strain A than strain B, this is not the case. Instead, this decrease on the plot is visible simply because the rate of vaccination (the rate into class R_{AV}) is not as large as the rate of infection for strain $B|A$ (the rate out of class R_{AV}). This explains why the max for $I_{B|A}$ is high while that of $I_{A|B}$ is only begins growing towards the end of the time period.

The graph (3, 10) (Figure 4f), has similarities and differences to (1.8, 3) and (1.8, 10). The vaccine classes R_{AV} and R_{BV} are similar, if not identical, to those in (1.8, 10) and reach their dosage limits at the same time ($t = 1.7$). The general trends of I_B and $I_{B|A}$ are also similar to those in (1.8, 10), and I_A and R_A are very small, just as in both (1.8, 3) and (1.8, 10). There is one major difference in the graph (3,10). R_B reaches a high peak (similarly to the other two graphs), but instead of holding fairly constant, it decreases significantly before reaching the end of the time period. In graphs (1.8, 3) and (1.8, 10), R_B remains at a high value because $I_{A|B}$ does not grow in the time allotted. This can be explained by the fact that in graph (3, 10) the $\beta_{A|B}$ value was increased. This allowed the class $I_{A|B}$ to reach its max quicker due to the decreasing number of people in class R_B. It should be noted that even though β_A was also increased, it could still not overcome the much large value of β_B, leaving the classes I_A and R_A to remain small.

5.2 Determining Vaccination Strategies

We created six contour plots to determine the minimum number of total infections that would occur over an outbreak by varying the two vaccination rates in our model (Figure 5). The rate of administration of vaccine A (ν_A) lies on the horizontal axis and the rate of administration of vaccine B lies on the vertical axis (ν_B). The contours show the total number of infections resulting in each of six R_0 value pairs. Table 1 shows the minimum number of infections in each situation.

(R_0^A, R_0^B)	min I	(ν_A, ν_B)
$(1.8, 1.8)$	57.1636	(8.5714, 8.3673)
$(1.8, 3)$	188.4582	(6.5306,10)
$(1.8, 10)$	179.7436	(0.2041,0)
$(3, 3)$	525.0718	(0,10)
$(3, 10)$	488.0554	(0.2041,0)
$(10, 10)$	889.2731	(0.1837,0)

Table 1: The minimum number of total infections at each pair of R_0 values for strains A and B. The first column lists the R_0 values. The second column gives the minimum number of total infections achieved from varying the vaccination rates. The third column gives the the vaccination rates A and B respectively required to result in the minimum number of total infections.

When $R_0 = 1.8$ for both strains (Figure 5a), the graph oscillates, reaching lower points near the $\nu_A = \nu_B$ line as ν_A and ν_B increase. The oscillation is discussed in section 6. Larger values of infections occur along the axes. The minimum number of infections is 57.1636, and occurs when $\nu_A = 8.5714$ and $\nu_B = 8.3673$. In actuality, the minimum should occur along the $\nu_A = \nu_B$ line, but the optimization scheme's grid spacing prevented it from finding it exact minimum. It is important to note that the graph is symmetric about the $\nu_A = \nu_B$ line because R_0 is the same for strains A and B. This same feature can be seen in the next two graphs in which $R_0 = 3$ and $R_0 = 10$ for both strains (Figures 5b,c).

When $R_0 = 3$ for both strains (Figure 5b) the graph still oscillates. In this case, the amplitude of the oscillations along the $\nu_A = \nu_B$ line are higher than in the previous plot. Here, the smallest value of infections occurs near the axes. The minimum value is 525.0718 and occurs when $\nu_A = 10$ and $\nu_B = 0$. Note that due to symmetry, the minimum also occurs at $\nu_A = 0$ and $\nu_B = 10$.

When $R_0 = 10$ for both strains (Figure 5c), the results turn out differently. The axis values were changed from 0 to 10 to 0 to 1. This range was chosen because the number of infections stops changing after $\nu = 0.5$ for both A and B. The minimum value of 889.2731 occurs when $\nu_A = 0.1837$ and $\nu_B = 0$. This pattern is due to the high β values for A and B. Again, due to symmetry, the minimum also occurs at $\nu_A = 0$ and $\nu_B = 0.1837$.

The contour plots of the remaining combinations of R_0 pairs (Figure 6d-f) each have different trends. For these non-symmetric graphs, the plots generally trend such that total infection numbers near the ν_A-axis are lower than along the ν_B axis. Note that strain A always has the lower R_0 values for these graphs. This means that when the strain with the lowest R_0 value is vaccinated against more quickly, then it results in fewer total infections.

For graph (1.8, 3) (Figure 6d), the minimum value is 188.4582, occurring when $\nu_A = 6.5306$ and $\nu_B = 10$. For graph (1.8, 10) (Figure 6e), it hits its minimum of 179.7436 at $\nu_A = 0.2041$ and $\nu_B = 0$. For graph (3, 10) (Figure 6f) it also hits its minimum of 488.0554 at $\nu_A = 0.2041$ and $\nu_B = 0$. Interestingly, the trend of this plot goes against the general rule stated previously. This time the lowest number of infections generally stays along the ν_B-axis while the highest number follows the ν_A-axis. This is similar to the situation encountered with graph (3,3), where the general trend of the other graphs is the opposite in this graph.

6 Discussion

Vaccines, when allocated optimally to a population through which multiple strains of the influenza virus are present, ultimately decrease the number of infections and the likelihood of an outbreak occurring. Looking at the population trend graphs (Figure 4), it is noted that despite varying R_0 values, vaccines administered at varying rates decrease the chance the virus will spread, even when the R_0 values imply that an outbreak should happen.

Finding the best allocation between the two vaccines and, thus, rates of vaccination is difficult. The contour plots (Figures 5a-f) reveal that no single vaccination strategy is superior in all scenarios. However, by dissecting the trends and further analyzing the plots, we can come up with a few general assumptions about optimal vaccination strategies.

The first feature to discuss is the oscillations in some of the contour plots. The total number of infections oscillates as the vaccination rates change as seen in the contour plots. As opposed to a curve with one local minimum, instead, the oscillations in many of the scenarios yield multiple local minima. This is the primary reason why we chose to avoid using a steepest-decent optimization scheme and instead to compute a large number of values of the objective function (the total number of infections), see Appendix for details.

Because of the numerous local minima in some of the graphs, it can be difficult to vaccinate at the optimal rate in practice. If the rates are not exactly attained, the number of total infections can change, often dramatically. It is in our best interest, then, to aim for a minimum value on the contour plots that is low, but not close enough to the threshold value to cause a dramatic effect on total number of infections. This reveals the delicacy of determining optimal vaccination rates and speaks to the importance of determining the basic reproductive number of each strain of the flu virus prior to and during the flu season to determine the best vaccination rates for each strain. It should be noted, though, that this could be an artifact of the construction of using constant vaccination rates in the model rather than using an impulse function, for instance, to model instantaneous vaccine delivery.

Another observed pattern is the optimal vaccination rates in all three cases when $R_0^B = 10$. The vaccination rates that yield the least number of infected individuals is when there is no vaccination against the stronger strain (B) and a very slow vaccination rate against the weaker strain (A). An R_0 of 10 creates such a high rate of infection that vaccinating against the stronger strain is simply too slow; delaying the administration of the vaccine for these virus strains preserves the number of vaccine doses available, so those who were not infected during the peak of infection then have a higher chance of being protected from the virus before exposure, thereby decreasing the total number of infection. However, with weaker strains of the virus, the rate of infection is significantly slower, making it easier to vaccinate many individuals before they are exposed or infected.

Finally, the last feature we will discuss is the behavior of the graph (3, 3) (Figure 5b). Both graphs (1.8, 1.8) and (10, 10) (Figure 5a,c) are symmetric with the lowest number of infections occurring along the $\nu_A = \nu_B$ line. While (3, 3) is also symmetric, the highest number of infections actually occur along the $\nu_A = \nu_B$ line. The minimum of $\nu_A = 10, \nu_B = 0$ indicates that it is optimal to vaccinate as quickly against one of the two strains as possible while ignoring the other strain. In this situation, the outbreak for one strain is largely stymied, while the other strain goes unchecked. This scenario results in a smaller total number of infections, as opposed to if the doses of vaccine were shared between the strains resulting in two smaller outbreaks.

From our research, we found that the optimal rate at which to vaccinate against multiple strains of a virus in a controlled population is largely dependent on both the magnitude of each R_0 and their comparative values. When the R_0 values of the two strains are identical, we observated that the optimal vaccination strategy varies from equal distribution and moderately fast vaccination (R_0=1.8) to one-sided vaccination as quick as possible (R_0=3) to one-sided vaccination slowly (R_0=10).

Clearly, our model is a simplification of an incredibly complex real-world process. Further

research could also look into more detailed scenarios including (1) vaccinations not being 100% effective, (2) more than two strains of a virus, (3) vaccinations that protect against multiple flu virus strains, at least partially, (4) limited accessibility of the vaccines to the population, and (5) utilizing an impulse function to model scenarios in which vaccination could happen immediately. Nevertheless, we believe our result that optimal vaccination strategies vary significantly based on the basic reproductive numbers of each viral strain could inform health care policies for vaccine administration.

7 References

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8 Appendix: Coding the Model

We used the software package `MATLAB` (Mathworks, Inc.) to create a series of programs to solve our model. We created 3 different files to completely run our model. The title of the file that initiated our model is FLUV.

First, in FLUV, we defined our parameters - the initial conditions of our virus and the population in which it is spread. For the entirety of our experiment, N remained at 1000 and was not altered. The number of vaccine doses was also kept consistent for each run at 400. All four of the gamma values stayed the same, as described in part 3. The values for γ_A and γ_B were kept at $\frac{1}{2}$, while the values for $\gamma_{A|B}$ and $\gamma_{B|A}$ were kept at $\frac{1}{4}$. As a reminder, the unit of γ is $time^{-1}$. The ν values were also kept consistent in this file. For purposes of simplicity, we kept both ν_A and ν_B values the same, at $\frac{1}{6}$. Again, as a reminder, units of ν are $time^{-1}$.

The parameters that we did change for each run of the model were the β values. The purpose of changing the β values was to give us R_0 values of 1.8, 3, and 10 (Table 2). As we changed our β values, we made sure to keep our β_A and β_B values bigger than our $\beta_{A|B}$ and $\beta_{B|A}$ values. We did this to model the situation in which it will be harder to contract the second strain of the flu once an individual has already recovered from the first. We also kept our γ_A and γ_B values bigger than our $\gamma_{A|B}$ and $\gamma_{B|A}$ values, as stated previously. We did this for a similar reason as the β values, except that we are modeling the fact that it will be easier to recover from the flu the first time and harder to recover once a person has already previously contracted and recovered from a different strain.

	β_A and β_B	$\beta_{A/B}$ and $\beta_{B/A}$	γ_A and γ_B	$\gamma_{A/B}$ and $\gamma_{B/A}$
$R_0 = 1.8$	$\frac{9}{10}$	$\frac{9}{20}$	$\frac{1}{2}$	$\frac{1}{4}$
$R_0 = 3.0$	$\frac{3}{2}$	$\frac{3}{4}$	$\frac{1}{2}$	$\frac{1}{4}$
$R_0 = 10.0$	5	$\frac{5}{2}$	$\frac{1}{2}$	$\frac{1}{4}$

Table 2: Values of γ and β that were used to give us each particular R_0 value. R_0 is given as $\frac{\beta}{\gamma}$

After setting the parameters, we set the time for our model to go from 0 to 30, increasing in increments of .01. These values could be any unit of time, from days to months. We did not specify the time unit. This was done in MATLAB by coding

```
t_of_choice = 0:.01:30;
```

Next we set the initial conditions of our population as the number of people in each class at time 0. We started with 998 people in the susceptible class and 1 person in both I_A and I_B. There were zero individuals in any of the other classes. Numerical solutions were computed by implementing a 4th-5th order Runge-Kutta method available in the package MATLAB. See documentation for ODE solvers.

```
[t1,y1] = ode45(@SIRIRmodel,t_of_choice, [998 1 1 0 0 0 0 0 0 0 0 0])
```

To model the situation in which the limit of vaccine doses had been reached, we needed to find the time value this occurred at, which we called 't_switch'.

```
i = 1;
while ((y1(i,11) < vac) && (i < length(t1)))
    i = i + 1;
end1
t_switch = t1(i) % This is the time value when the total number of people vaccinated is
                 % about to hit the max.
new_t = t_switch:.01:30;
nuA = 0; nuB = 0;
[t2,y2] = ode45(@SIRIRmodel,new_t,y1(i,:));

t_total = [t1(1:(i-1));t2];
y_total = [y1(1:(i-1),:);y2];
```

Essentially, what we did is run the model twice - first with vaccines then without them. The "while" statement tells MATLAB to run the model that we initially set while vac is still less than 400. Then, "t-switch" occurs right when $vac = 400$. We then tell MATLAB to run our ODE model without any inclusion of vaccines, which we called the SIRIRmodel. The SIRIRmodel starts exactly where FLUV left off. The total of each of the models was then added together in the end to plot the overall situation (Figures 3a-i).

```
figure(1)
plot(t_total,y_total(:,1),t_total,y_total(:,2),t_total,y_total(:,3),...
t_total,y_total(:,4),t_total,y_total(:,5),t_total,y_total(:,6),...
t_total,y_total(:,7),t_total,y_total(:,9),t_total,y_total(:,10))
title('Population Trend','fontsize',27)
xlabel('Time','fontsize',22)
ylabel('People','fontsize',22)
legend('S','Ia','Ib','Ra','Rb','Iba','Iab','Rav','Rbv')
```

```
set(legend,'fontsize',22)

figure(2)
plot(t_total,y_total(:,11),t_total,y_total(:,9),t_total,y_total(:,10))
title('Vaccine Effects')
xlabel('Time')
ylabel('People')
legend('Vac', 'Rav', 'Rbv')

sum(y_total(end,1:10))
```

As we have already stated, our goal is to find the optimal rate of administration of two different vaccines into a population in which two different strains of the influenza virus exists. We define this 'optimal rate' as the rate at which each vaccine is administered that resulted in the fewest number of infections. Keep in mind that the term 'infection' refers to an individual getting sick from a strain of the virus. Because our model allows one person to get infected with both strains, the highest possible number of infections that can result is 2000 (1000 people getting infected twice).

We found that the best possible way to find our optimal rate was to run the model many times with many different combinations of vaccination rates. In this way, we were able to see the result (number of infections) from each run, and compare them to the results of other runs. We then found the smallest number of infections and the two vaccination rates that resulted in this number. However, we understood that with so many vaccination rate possibilities, we decided not to run the model manually. Instead, we set up a loop in `MATLAB`.

To run a loop, we first had to create a function for the loop to call and run multiple times. This function we called 'FLUVCONTROL' and is simply our initial model that we used to set up the situation. We set up the function as:

```
[totsick] = FLUVCONTROL(nuA,nuB)
```

All this is saying is that FLUVCONTROL is a function of our two vaccination rates, ν_A and ν_B, and that the output of the function is the total number of infections that occur. As described earlier, this was found by summing up the total number of individuals entering each infected class, I_A, I_B, $I_{A|B}$, and $I_{B|A}$.

The initial parameters were all set to remain constant except for ν_A and ν_B, which was given by the calling function. The rest of the model remains the same as described in section 3.

We set up the loop with a matrix. In the loop, we set both ν_A and ν_B to have 50 different values. We then assigned those 50 values to be between the two rates of 0 and 10 with the entry:

```
nuA = linspace(0,10,50);
nuB = linspace(0,10,50);
```

With the two terms defined, we then assigned the results to line up in a matrix corresponding to the combination of vaccination rates from which it came. In other words, we set up a matrix with 2500 different entries, with the 50 ν_A values as columns and the 50 ν_B values as rows. This was done by

```
Results = zeros(length(nuA),length(nuB));
```

The loop was then set up to call the model and run it using the different vaccination rate values:

```
For i=1:length(nuA)
  For j=1:length(nuB)
    Results(i,j) = FLUVCONTROL(nuA(i),nuB(j));
  End
End
```

This programmed the loop to run the model and assign the results in their corresponding spots in the matrix. The loop placed the result of the model run with vaccination rate $\nu_A = 0$ and $\nu_B = 0$ in the entry (1,1); the result of the model run with $\nu_A = 0.2$ and $\nu_B = 0$was placed in (2,1) and so on.

We also decided that we did not think reading through a 50×50 matrix and attempting to find the lowest number was realistic nor an adequate use of time. So, to find this result, we set up two different methods.

The first function was to let MATLAB find the minimum, give us the resulting number, and also give us the location in the matrix from where it was found. To do this, we assigned the 50×50 matrix as the letter 'A'. We then used the 'min' function to find the lowest entry:

```
A = [results];
OURMIN = min(min(A))
For i=1: length(nuA)
    For j=1: length(nuB)
        If (OURMIN == A(i,j))
            THEMINDIMENSIONSARE = [i,j];
        END
    END
END
```

This function gave us the smallest entry (the smallest number of infections), and where the smallest entry was found in the matrix (corresponding to the ν_A and ν_B values that gave the results).

The second method we used to find the lowest entry was a contour plot of the results. This gave us the opportunity not only to visually see the lowest value and where it was, but also to analyze the results and the pattern that was created with the different vaccination rate values. To do this, we used the "contour" function.

```
[C,h] = contour(nuA,nuB,results)
set(h,'ShowText','on','TextStep',get(h,'LevelStep'))
```

This function plotted, labeled, and color coded our results (Figures 4a-i).

Just as in our file FLUV, we repeated this process for R_0 values of 1.8, 3, and 10.

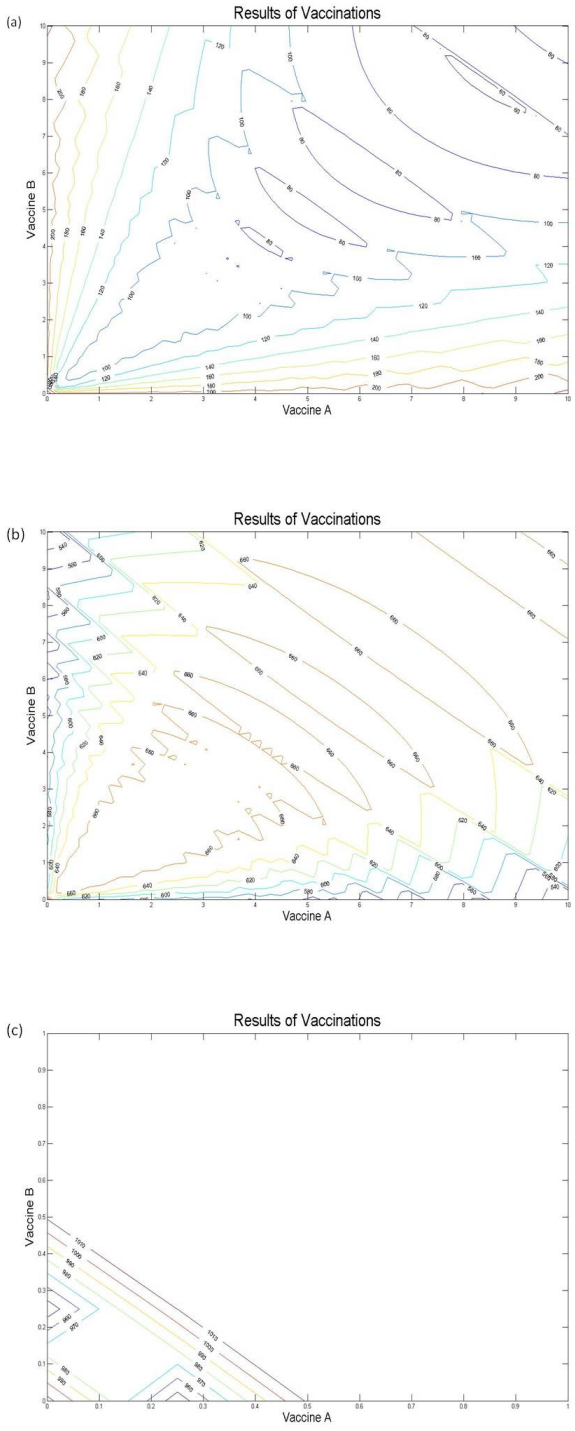

Figure 5: Contour plots where the height of the contour is the total number of infections from an outbreak with variable vaccination rates, ν_A along the horizontal axis and ν_B along the vertical axis. Panel (a) is when $R_0^A = R_0^B = 1.8$. Panel (b) is $R_0^A = R_0^B = 3.0$. Panel (c) is $R_0^A = R_0^B = 10.0$.

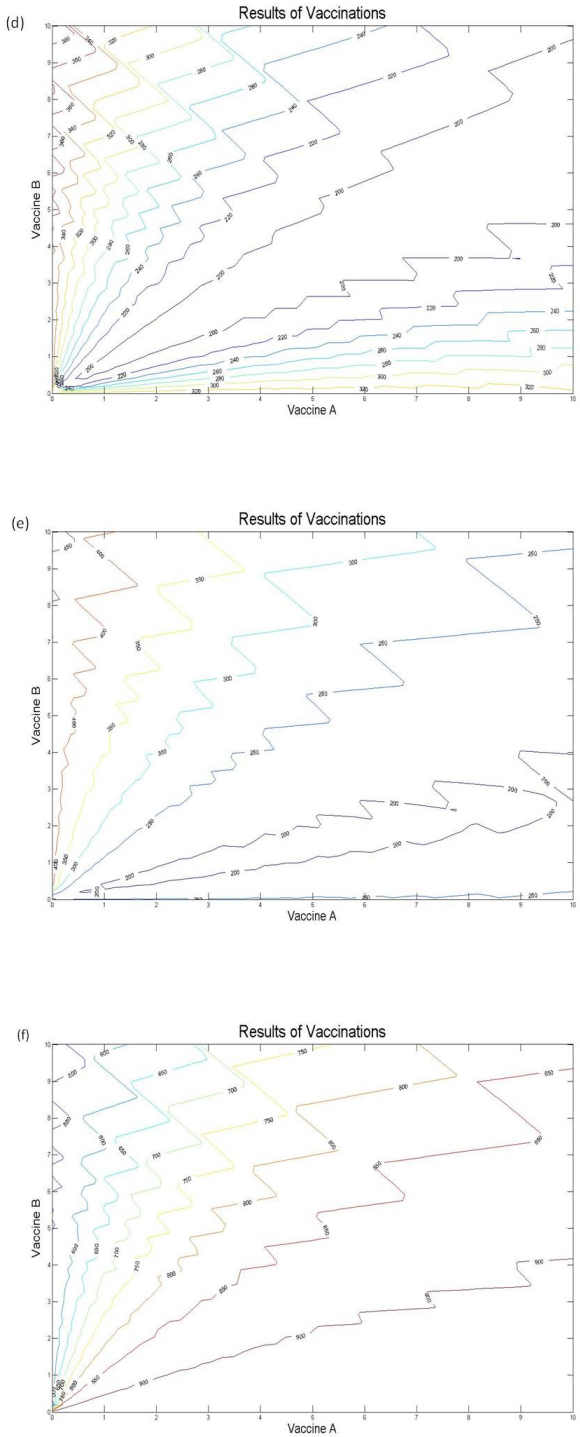

Figure 6: Contour plots where the height of the contour is the total number of infections from an outbreak with variable vaccination rates, ν_A along the horizontal axis and ν_B along the vertical axis. Panel (d) is $R_0^A = 1.8$ and $R_0^B = 3.0$. Panel (e) is $R_0^A = 1.8$ and $R_0^B = 10.0$. Panel (f) is $R_0^A = 3.0$ and $R_0^B = 10.0$.